451854 Vd rw 6/23

**STIC-ILL**

**From:** Baskar, Padmavathi
**Sent:** Monday, June 23, 2003 12:33 PM
**To:** STIC-ILL
**Subject:** 09/300612, please consider this as rush

Bone "The Pathogenesis of Sepsis" Ann Int Med 115(6) 457-469 1991.
Guyton "Textbook of Medical Physiology" 8th Ed 269-271 1991.
Mousstach e et al "Mechanisms of Resistance of the Opossum to Some Snake Venoms" Toxicon 17(Suppl. 1) 130 1979.
Domont et al. "Natural Anti-Snake Venom Proteins" Toxicon 29(10) 1183-1194 1991.
Perales et al "Neutralization of the Oedematogenic activity of Bothrops Jararaca venom on the Mouse Paw by an antibothropic
Fraction Isolated from Opossum serum" Agents Actions 37(3-4) 250-259 1992.
Tomihara et al. "Purification of Three Antihemorrhagic Factors From The Serum of A Mongoose" Toxicon 25(6) 685-689 1987.
Perates et al. "Anti Snake Venom Protein from Didelphidae" Abstract 10th World Congress. Toxicon 30(5-6) 543 1992.
Menchaca et al. "The Purification & Characterization of An Antihemerrhagic Factor in Opossum Serum" Toxicon 19(5) 623-632 1981.

Toxicon 14(4) 337-340, 1976

Tarng et al , Toxicon 24(6) 567-573, 1986.

Toxicon 34(11-12) 1313-6, 1996.

**Toxicon 36(10) 1451-9, 1998.**
**HIGH TECH SEPARATIONS NEWS 1996, V9,N4, SEP1996**

Toxicon 37(6) 949-954, 1999.

Toxicon 37(5) 703-728, 1999.

biochimica et biophysica acta 1995, 1245 (2) 232-8

Padma Baskar
Art Unit 1645
Patent Examiner/Biotechnology
CM-1, 8E-13
703-308-8886

LC
6/24
SMP
Completed
0
6
1.20

# Textbook of MEDICAL PHYSIOLOGY

## Eighth Edition

**Arthur C. Guyton, M.D.**
Professor
Department of Physiology and Biophysics
University of Mississippi School of Medicine

1991
W.B. SAUNDERS COMPANY
Harc urt Brace J vanovich, Inc.
Philadelphia ■ London ■ Toronto ■ Montreal ■ Sydney ■ Tokyo

W. B. Saunders Company
Harcourt Brace Jovanovich, Inc.

The Curtis Center
Independence Square West
Philadelphia, PA 19106



**Library of Congress Cataloging-in-Publication Data**

Guyton, Arthur C.
Textbook of medical physiology/Arthur C. Guyton.—8th ed.
p. cm.
Includes bibliographical references.
Includes index.
ISBN 0-7216-3087-1
1. Human physiology. 2. Physiology, Pathological. I. Title.
[DNLM: 1. Physiology. QT 104 G992-]
QP34.5.G9 1991
612—dc20 90-8653
CIP

Listed here are the latest translated editions of this book together with the language of each translation and the publisher.

Japanese (*4th Edition*)—Hirokawa Publishing Compay, Tokyo, Japan
Serbo-Croatian (*4th Edition*)—Medicinska Knjiga, Belgrade, Yugoslavia
Italian (*4th Edition*)—Piccin Editore, Padova, Italy
Spanish (*7th Edition*)—Nueva Editorial Interamericana S.A. de C.V., Mexico City, Mexico
Persian (*7th Edition*)—Sherkat Sahami "TCHEHR," Tehran, Iran
Portuguese (*6th Edition*)—Editora Interamericana Ltda., Rio de Janeiro, Brazil

*Editor:* Martin J. Wonsiewicz
*Developmental Editor:* Rosanne Hallowell
*Designer:* Joan Wendt
*Production Manager:* Peter Faber
*Manuscript Editor:* Jessie Raymond
*Mechanical Artist:* Risa Clow
*Illustration Coordinator:* Brett MacNaughton
*Indexer:* Ann Kassar
*Cover Designer:* Michelle Maloney

TEXTBOOK OF MEDICAL PHYSIOLOGY, Eighth Edition ISBN 0-7216-3087-1



Printed in the United States of America.

Last digit is the print number: 9 8 7 6 5 4 3 2 1

an increase in vascular capacity or a decrease in blood volume *reduces the mean systemic filling pressure*, which in turn reduces the venous return to the heart. Diminished venous return caused by vascular dilatation is often called "venous pooling" of blood.

**Causes of Neurogenic Shock.** Some of the different factors that can cause loss of vasomotor tone include the following:

1. *Deep general anesthesia* often depresses the vasomotor center enough to cause vasomotor collapse, with resulting neurogenic shock.
2. *Spinal anesthesia*, especially when this extends all the way up the spinal cord, blocks the sympathetic outflow from the nervous system and is a common cause of neurogenic shock.
3. *Brain damage* is often a cause of vasomotor collapse. Many patients who have had brain concussion or contusion of the basal regions of the brain develop profound neurogenic shock. Also, even though short periods of medullary ischemia cause extreme vasomotor activity, prolonged ischemia can cause inactivation of the vasomotor neurons and can cause development of severe neurogenic shock.

**Vasovagal Syncope—Emotional Fainting.** The circulatory collapse that results from "emotional" fainting usually is not caused by vasomotor failure but instead by strong emotional activation of parasympathetic signals to slow the heart and sympathetic signals to dilate the peripheral vasculature, thereby decreasing cardiac output and arterial pressure. Therefore, the fainting that results from an emotional disturbance is called *vasovagal syncope* to differentiate it from other types of fainting that result from other causes of reduced cardiac output.

## ANAPHYLACTIC SHOCK

"Anaphylaxis" is an allergic condition in which the cardiac output and arterial pressure often fall drastically. This is discussed in Chapter 34. It results primarily from an antigen-antibody reaction that takes place immediately after an antigen to which the person is sensitive has entered the circulation. One of the principal effects is to cause the *basophils* in the blood and the *mast* cells in the pericapillary tissues to release *histamine* or a *histamine-like substance*. The histamine in turn causes (1) an increase in vascular capacity because of venous dilatation, (2) dilatation of the arterioles with resultant greatly reduced arterial pressure, and (3) greatly increased capillary permeability with rapid loss of fluid and protein into the tissue spaces. The net effect is a great reduction in venous return and often such serious shock that the person dies within minutes.

Intravenous injection of large amounts of histamine causes "histamine shock," which has characteristics almost identical with those of anaphylactic shock, though usually less severe.

## SEPTIC SHOCK

The condition that was formerly known by the popular name of "blood poisoning" is now called *septic shock* by most clinicians. This simply means widely disseminated infection to many areas of the body, with the infection being borne through the blood from one tissue to another and causing extensive damage. Actually, there are many different varieties of septic shock because of the many different types of bacterial infection that can cause it and also because infection in one part of the body will produce different effects from those caused by infection elsewhere in the body.

Septic shock is extremely important to the clinician because this type of shock, more frequently than any other kind of shock besides cardiogenic shock, causes patient death in the modern hospital. Some of the typical causes of septic shock include

1. Peritonitis caused by spread of infection from the uterus and fallopian tubes, frequently resulting from instrumental abortion.
2. Peritonitis resulting from rupture of the gut, sometimes caused by intestinal disease and sometimes by wounds.
3. Generalized infection resulting from spread of a simple skin infection, such as streptococcal or staphylococcal infection.
4. Generalized gangrenous infection resulting specifically from gas gangrene bacilli, spreading first through the tissues themselves and finally by way of the blood to the internal organs, especially to the liver.
5. Infection spreading into the blood from the kidney or urinary tract, often caused by colon bacilli.

**Special Features of Septic Shock.** Because of the multiple types of septic shock, it is difficult to categorize this condition. However, some features are

1. High fever.
2. Marked vasodilation throughout the body, especially in the infected tissues.
3. High cardiac output in perhaps half of the patients, caused by vasodilation in the infected tissues and also by high metabolic rate and vasodilation elsewhere in the body resulting from bacterial toxin stimulation of cellular metabolism and from the high body temperature.
4. Sludging of the blood, presumably caused by red cell agglutination in response to degenerating tissues.
5. Development of microclots in widespread areas of the body, a condition called *disseminated intravascular coagulation*. Also, this causes the clotting factors to be used up so that hemorrhages occur into many tissues, especially into the gut wall and into the intestinal tract.

In the early stages of septic shock, the patient usually does not have signs of circulatory collapse but, instead, only signs of the bacterial infection itself. However, as the infection becomes more severe, the circulatory system usually becomes involved either directly or as a secondary result of toxins from the bacteria, and *there finally comes a point at which deterioration of the circulation becomes progressive in the same way that progression occurs in all other types of shock. Therefore, the end-stages of septic shock are not greatly different from the end-stages of hemorrhagic shock*, even though the initiating factors are markedly different in the two conditions.

**Endotoxin Shock.** A special type of septic shock is known as endotoxin shock. It frequently occurs when a large segment of the gut becomes strangulated and loses most of its blood supply. The gut rapidly becomes gangrenous, and the bacteria in the gut multiply rapidly. Most of these bacteria are so-called "gram-negative" bacteria, mainly colon bacilli, that contain a toxin called *endotoxin*. Another condition that also frequently causes colon bacilli septicemia is extension of urinary tract infections into the blood.

On entering the circulation, endotoxin causes an effect very similar to that of anaphylaxis, often resulting in severe shock. Also, further compounding the circulatory depression is a direct effect of endotoxin on the heart to decrease myocardial contractility.

## EFFECTS OF SHOCK ON THE BODY

**Decreased Metabolism and Cellular Deterioration in Hypovolemic Shock.** In hypovolemic shock, the decreased cardiac output reduces the delivery of both oxygen and other nutrients to the tissues. This in turn reduces the metabolism of virtually all cells of the body, leading to multiple types of cellular damage, including (1) decreased ability of the mitochondria to synthesize ATP, (2) decreased ability of the cell's membrane pump to keep the sodium concentration low and the potassium concentration high inside the cell, (3) depressed processing of nutrients by the cell's metabolic machinery, and (4) eventual rupture of many lysosomes, releasing digestive enzymes within the cells that cause intracellular destruction and even death of cells. Obviously, all these effects lead to still greater cellular deterioration and further decrease in total bodily metabolism. Usually a person can continue to live for only a few hours if the cardiac output falls to as low as 40 per cent of normal.

**Muscular Weakness.** One of the earliest symptoms of shock is severe muscular weakness that is also associated with profound and rapid fatigue whenever patients attempt to use their muscles. This obviously results from the diminished supply of nutrients — especially oxygen — to the muscles.

**Body Temperature.** Because of the depressed metabolism in shock, the amount of heat liberated in the body is reduced (except in septic shock in which the infection may cause an opposite effect). As a result, the body temperature tends to decrease if the body is exposed to even the slightest cold.

**Mental Function.** In the early stages of shock the person is usually conscious, though signs of mental haziness may be noted. As the shock progresses, the person falls into a state of stupor, and in the last stages of shock even the subconscious mental functions, including vasomotor control and respiration, fail.

A person who recovers from shock usually exhibits no permanent impairment of mental functions.

**Reduced Renal Function and Renal Deterioration.** Even the slight decreases in cardiac output and arterial pressure that occur in the early stages of shock greatly diminish or even abolish urine output, because the glomerular pressure falls below the critical level required for filtration. Other renal effects are discussed in Chapters 26 through 29. This retention of fluid by the kidneys is usually helpful in shock, for it aids in preventing further diminishment of blood volume.

In the late stages of shock, however, the renal tubular epithelial cells deteriorate extremely rapidly because normally they have a very high metabolism and require large amounts of nutrients. The result is severe *tubular necrosis* with tubular cell death and sloughing and blockage of the tubules. Therefore, even though a person might survive the shock itself, the damage often subsequently causes renal shutdown, with death occurring a week or so later because of uremia.

## PHYSIOLOGY OF TREATMENT IN SHOCK

### REPLACEMENT THERAPY

**Blood and Plasma Transfusion.** If a person is in shock caused by hemorrhage, the best possible therapy is usually transfusion of whole blood. If the shock is caused by plasma loss, the best therapy is administration of plasma; when dehydration is the cause, administration of the appropriate electrolytic solution can correct the shock.

Unfortunately, whole blood is not always available, such as under battlefield conditions. However, plasma can usually substitute adequately for whole blood because it increases the blood volume and restores normal hemodynamics. Plasma cannot restore a normal hematocrit, but the human can usually stand a decrease in hematocrit to about one-third normal before serious consequences result if the cardiac output is adequate. Therefore, in acute conditions it is reasonable to use plasma in place of whole blood for treatment of hemorrhagic and most other types of hypovolemic shock.

Sometimes plasma also is unavailable. In these instances, various *plasma substitutes* have been developed that perform almost exactly the same hemodynamic functions as plasma. One of these is the following:

**Dextran Solution as a Plasma Substitute.** The principal requirement of a truly effective plasma substitute is that it remain in the circulatory system — that is, not filter through the capillary pores into the tissue spaces. In addition, the solution must be nontoxic and must contain appropriate electrolytes to prevent derangement of the extracellular fluid electrolytes on administration. To remain in the circulation the plasma substitute must contain some substance that has a large enough molecular size to exert colloid osmotic pressure.

One of the most satisfactory substances that has been developed thus far for this purpose is dextran, a large polysaccharide polymer of glucose. Certain bacteria secrete dextran as a by-product of their growth, and commercial dextran is manufactured by a bacterial culture procedure. By varying the growth conditions of the bacteria, the molecular weight of the dextran can be controlled to the desired value. Dextrans of appropriate molecular size do not pass through the capillary pores and, therefore, can replace plasma proteins as colloid osmotic agents.

Fortunately, few toxic reactions have been observed when using dextran to provide colloid osmotic pressure; therefore, solutions of this substance have proved to be a satisfactory substitute for plasma in much fluid replacement therapy.

### TREATMENT OF SHOCK WITH SYMPATHOMIMETIC DRUGS

A *sympathomimetic drug* is a drug that mimics sympathetic stimulation. These drugs include norepinephrine, epinephrine, and a large number of long-acting drugs that have the same effects as epinephrine and norepinephrine.

In two types of shock, sympathomimetic drugs have proved to be especially beneficial. The first of these is *neurogenic shock*, in which the sympathetic nervous system is severely depressed. Administering a sympathomimetic drug takes the place of the diminished sympathetic activity and can often restore full circulatory function.

The second type of shock in which sympathomimetic drugs are very valuable is *anaphylactic shock*, in which histamine plays a prominent role. The sympathomimetic drugs have a vasoconstrictor effect that opposes the vasodilating effect of histamine. Therefore, either norepinephrine or another sympathomimetic drug is often lifesaving.

Unfortunately, sympathomimetic drugs have not proved to be very valuable in hemorrhagic shock. The reason is that in this type of shock the sympathetic nervous system has

almost always already become maximally activated by the circulatory reflexes, and so much norepinephrine and epinephrine are circulating in the blood that the sympathomimetic drugs have essentially no additional beneficial effect.

### OTHER THERAPY

**Tr atm nt by th Head-Down Position.** When the pressure falls too low in most types of shock, especially hemorrhagic and neurogenic shock, placing the patient with the head as much as a foot lower than the feet will help tremendously in promoting venous return and thereby increasing cardiac output. Therefore, this is the first essential in the treatment of many types of shock.

**Oxygen Therapy.** Since the major deleterious effect of most types of shock is too little delivery of oxygen to the tissues, giving the patient oxygen to breathe can be of benefit in some instances. However, this frequently is of far less value than one might expect because the problem usually is not inadequate oxygenation of the blood in the lungs, but inadequate transport of the blood after it is oxygenated.

**Treatment With Glucocorticoids.** Glucocorticoids are frequently given to patients in severe shock for several reasons: (1) Experiments have shown empirically that glucocorticoids frequently increase the strength of the heart in the late stages of shock; (2) glucocorticoids stabilize the lysosomal membranes and prevent release of lysosomal enzymes into the cytoplasm of the cells, thus preventing deterioration from this source; (3) glucocorticoids might also aid in the metabolism of glucose by the severely damaged cells.

## CIRCULATORY ARREST

A condition closely allied to circulatory shock is circulatory arrest, in which all blood flow completely stops. This occurs frequently on the surgical operating table as a result of *cardiac arrest* or of *ventricular fibrillation.*

Ventricular fibrillation can usually be stopped by strong electroshock of the heart, the basic principles of which were described in Chapter 13.

Cardiac arrest usually results from too little oxygen in the anesthetic gaseous mixture or from a depressant effect of the anesthesia itself. A normal cardiac rhythm can usually be restored by removing the anesthetic and then applying cardiopulmonary resuscitation procedures for a few minutes while supplying the patient's lungs with adequate quantities of ventilatory oxygen.

### Effect of Circulatory Arrest on the Brain

A special problem in circulatory arrest is to prevent detrimental effects in the brain as a result of the arrest. In general, 4 to 5 minutes of circulatory arrest causes permanent brain damage in over half the patients. Circulatory arrest for as long as 10 minutes almost universally destroys most, if not all, of the mental powers.

For many years it was taught that this detrimental effect on the brain was caused by the cerebral hypoxia that occurs during circulatory arrest. However, experiments have shown that, if blood clots are prevented from occurring in the blood vessels of the brain, this will also prevent the very rapid deterioration of the brain during circulatory arrest. For instance, in one animal experiment, all of the animal's blood was removed from the blood vessels at the beginning of circulatory arrest and then replaced at the end of the circulatory arrest, so that no intravascular blood clotting could occur. In these, the brain was able to withstand up to 30 minutes of circulatory arrest without any permanent brain damage. Also, administration of heparin or streptokinase prior to cardiac arrest was shown to increase the survivability of the brain two to four times as long as is usually the case. Therefore, it is likely that the severe brain damage that occurs following circulatory arrest results mainly from permanent blockage of many small or even large blood vessels by blood clots, thus causing prolonged ischemia and eventual death of the neurons.

## REFERENCES


Achauer, B. M.: Management of the Burned Patient. East Norwalk, Conn., Appleton & Lange, 1987.

Bernton, E. W., et al: Opioids and neuropeptides: Mechanisms in circulatory shock. Fed. Proc., 44:190, 1985.

Bond, R. F., and Johnson, G., III: Vascular adrenergic interactions during hemorrhagic shock. Fed. Proc., 44:281, 1985.

Braunwald, E. (ed.): Heart Disease. A Textbook of Cardiovascular Medicine. Philadelphia, W. B. Saunders Co., 1988.

Crowell, J. W., and Guyton, A. C.: Evidence favoring a cardiac mechanism in irreversible hemorrhagic shock. Am. J. Physiol., 201:893, 1961.

Crowell, J. W., and Smith, E. E.: Oxygen deficit and irreversible hemorrhagic shock. Am. J. Physiol., 206:313, 1964.

Filkins, J. P.: Monokines and the metabolic pathophysiology of septic shock. Fed. Proc., 44:300, 1985.

Franklin, J., and Doelp, A.: Shocktrauma. New York, St. Martin's Press, 1980.

Guyton, A. C., and Crowell, J. W.: Dynamics of the heart in shock. Fed. Proc., 20:51, 1961.

Guyton, A. C., et al.: Cardiac Output and Its Regulation. Philadelphia, W. B. Saunders Co., 1973.

Heffernan, J. J., et al.: Clinical Problems in Acute Care Medicine. Philadelphia, W. B. Saunders Co., 1989.

Intensive Care of the Surgical Cardiopulmonary Patient. Chicago, Year Book Medical Publishers, 1983.

Jamieson, G. A., and Greenwalt, T. J. (eds.): Blood Substitutes and Plasma Expanders. New York, A. R. Liss, 1978.

Jones, C. E., et al.: Cardiac output and physiological mechanisms in circulatory shock. In MTP International Review of Science: Physiology, Vol. 1. Baltimore. University Park Press, 1974, p. 233.

Jones, C. E., et al.: A cause-effect relationship between oxygen deficit and irreversible hemorrhagic shock. Surgery, 127:93, 1968.

Jones, C. E., et al.: Significance of increased blood uric acid following extensive hemorrhage. Am. J. Physiol., 214:1374, 1968.

Kovach, A. G. B., and Sandor, P.: Cerebral blood flow and brain function during hypotension. Annu. Rev. Physiol., 38:571, 1976.

Lefer, A. M.: Eicosanoids as mediators of ischemia and shock. Fed. Proc., 44:275, 1985.

Lefer, A. M., and Martin, J.: Relationship of plasma peptides to the myocardial depressant factor in hemorrhagic shock in cats. Circ. Res., 26:59, 1970.

Luce, J. M., and Pierson, D. J.: Critical Care Medicine. Philadelphia, W. B. Saunders Co., 1988.

McCord, J. M.: Oxygen-deprived free radicals in postischemic tissue injury. N. Engl. J. Med., 312:159, 1985.

Movat, H. Z.: Microcirculation in disseminated intravascular coagulation induced by endotoxins. In Renkin, E. M., and Michel, C. C. (eds.): Handbook of Physiology. Sec. 2 Vol. IV. Bethesda, American Physiological Society, 1984, p. 1047.

Rothe, C. F., et al.: Control of total vascular resistance in hemorrhagic shock in the dog. Circ. Res., 12:667, 1963.

Schmid-Schönbein, H., and Teitel, P. (eds.): Basic Aspects of Blood Trauma. Hingham, Mass., Kluwer Boston, 1979.

Shoemaker, W. C., et al. (eds.): Society of Critical Care Medicine, The Textbook of Critical Care. Philadelphia, W. B. Saunders Co., 1988.

Sibbald, W. J. (ed.): Synopsis of Critical Care. Baltimore, Williams & Wilkins, 1988.

Smith, E. E., and Crowell, J. W.: Effect of hemorrhagic hypotension on oxygen consumption of dogs. Am. J. Physiol., 207:647, 1964.

Tintinalli, J. E.: Emergency Medicine: A Comprehensive Study Guide. 2nd Ed. New York, McGraw-Hill Book Co., 1988.

Winkelman, J. L.: Essentials of Basic Life Support. Minneapolis, Burgess, 1981.